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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/625,073	07/22/2003	Mark I. Greene	4040/1K201US2	9446

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EXAMINER	
WILLIAMS, LEONARD M	

ART UNIT	PAPER NUMBER
1617	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/625,073	GREENE ET AL.	
	Examiner	Art Unit	
	Leonard M. Williams	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-17 is/are pending in the application.

4a) Of the above claim(s) 6-17 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-5 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 3/24/06, 12/06/04, 7/22/03.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Election/Restrictions

Applicant's election with traverse of the species Formula IA in the reply filed on 06/18/2007 is acknowledged. The traversal is on the ground(s) that there is no search burden for searching all the compounds of Formulas I-XII (and their independent species contained therein). This is not found persuasive because Formulas I-XII are drawn to distinct and unrelated structures/compounds that require individual non-overlapping searches and thus constitute a burden. Further Formula I is drawn to several individual structures and a species election for search purposes is appropriate in such instances.

The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5 are rejected under 35 U.S.C. 1 12, first paragraph, because the specification, while being enabling for a method of treating patients who have diseases characterized by bone loss comprising administering an amount of TRANCE/RANK inhibitors, wherein said inhibitors are selected from known TRANCE/RANK inhibitors as described in the prior art, does not reasonably provide enablement for a method of

treating patients who have diseases characterized by bone loss comprising administering an amount of TRANCE/RANK inhibitors, wherein said inhibitors are selected from Formula I (and in particular the species IA). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the ad; (4) the predictability or unpredictability of the ad; (5) the breadth of the claims', (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1) The Nature of the Invention:

The rejected claims are drawn to a method of treating patients who have diseases characterized by bone loss comprising administering an amount of TRANCE/RANK inhibitors effective to inhibit osteoclastogenesis and/or osteoclast function.

(2) Breadth of the Claims:

The breadth of the claims are exceptionally broad encompassing a method of treating patients who have diseases characterized by bone loss comprising administering to said patient any TRANCE/RANK inhibitor effective to inhibit osteoclastogenesis and/or osteoclast function.

(3) Guidance of the Specification:

The guidance of the specification as to a method of treating patients who have diseases characterized by bone loss comprising administering an amount of TRANCE/RANK inhibitors effective to inhibit osteoclastogenesis and/or osteoclast function is limited. On pages 40-55 of the specification a series of chemical structures covering Formulas I-XII are detailed. On pages 37-39

Compounds possessing other activities are not described in an enabling fashion.

(4) Working Examples:

The applicant provides two working examples. Example I on pages 37-38 of the specification, details the use of therapeutic peptidomimetics that interfere with the TNF/TNF receptor interaction as developed by Takasaki et al. A particular peptidomimetic (WP9QY) that inhibits osteoclastogenesis by acting as a TRANCE/RANK inhibitor is disclosed in an *in vitro* assay. No other compounds are described.

Example 2 describes the identification of the formation of osteoclasts via an *in vitro* assay wherein a positive control is osteoprotegerin (OPG). Thus OPG is a TRANCE/RANK inhibitor. The *in vitro* assay is based upon Nicholson et al. (see page 39 of specification).

(5) State/predictability of the Art:

The state of the art regarding a method of treating patients who have diseases characterized by bone loss comprising administering an amount of TRANCE/RANK inhibitors effective to inhibit osteoclastogenesis and/or osteoclast function is limited.

In a paper by Simonet et al. (Osteoprotegerin: A Novel Secreted Protein Involved in the Regulation of Bone Density, Cell, 1997, vol. 89, pp. 309-319), a novel secreted glycoprotein from the TNF superfamily was identified and called osteoprotegerin (OPG). In vivo, hepatic expression of OPG in transgenic mice results in a profound yet non-lethal ostepetrosis, coincident with a decrease in later stages of osteoclast differentiation. The same effect was seen when OPG was administered to normal mice. *In vitro* OPG blocked osteoclastogenesis in a dose-dependent manner. Simonet et al. demonstrate that OPG can act as a soluble factor in the regulation of bone mass and imply a utility in the treatment of osteoporosis associated with increased osteoclast activity (see summary page 309).

In EP0784093, Boyle et al. describe a secreted polypeptide, termed osteoprotegerin, which is a member of the TNF superfamily, involved in the regulation of bone metabolism (see abstract). On page 3, Boyle et al. describe that methods of

treating bone diseases such as osteoporosis, hypercalcemia, Paget's disease of bone, and bone loss due to rheumatoid arthritis or osteomyelitis are possible by administration of the polypeptides and/or via anti-sense or gene therapy. Pharmaceutical compositions comprising OPG nucleic acids and polypeptides are also encompassed.

Mbalaviele discloses, in the abstract of US Patent No. 6239157, a method of inhibiting the differentiation of CD34+ cells into osteoclasts by treating the cells with a peroxisome proliferator-activted receptor-γ (PPARγ) agonist. In col. 1 lines 35-55, Mbalaviele teaches that there is provided a process for treating osteoporosis by administering an amount of a PPARγ agonist. In col. 2 lines 60-68, Mbalaviele teaches that suitable PPARγ agonists include ciglitazone, pioglitazone, troglitazone, 15-deoxy-$\Delta^{12,14}$-prostaglandin-J2 and indomethacin.

Baker et al. teaches, the abstract of US Patent No. 6171860, antisense compounds and compositions and methods of using such for inhibiting the expression of RANK. In col. 2 lines 9-30, Baker et al. teach that RANK is essential to signaling pathways involved in bone morphogenesis, specifically the process of osteoclast differentiation.

Thus the state of the art is limited primarily to therapeutic polypeptides (OPG) and anti-sense compounds and compositions (directed toward inhibition of RANK expression) for the treatment of diseases characterized by bone loss comprising administering an amount of TRANCE/RANK inhibitors effective to inhibit osteoclastogenesis and/or osteoclast function. PPARγ agonists while inhibiting

osteoclastogenesis, are not clearly demonstrated to act through the inhibition of TRANCE/RANK.

No small molecules useful for the treatment of diseases characterized by bone loss comprising administering an amount of TRANCE/RANK inhibitors effective to inhibit osteoclastogenesis and/or osteoclast function have been found in the prior art.

(6) The Quantity of Experimentation Necessary:

The instant claims read on a method of treating patients who have diseases characterized by bone loss comprising administering to said patient *any* TRANCE/RANK inhibitor effective to inhibit osteoclastogenesis and/or osteoclast function. As discussed above, the specification fails to provide sufficient support for agents other than peptidomimetic (WP9QY) and OPG. The prior art provides support for anti-sense agents useful in the inhibition of RANK expression. Applicant fails to provide information sufficient to practice the claimed invention, absent undue experimentation (i.e. testing all small molecule agents described in methods of treating patients having diseases characterized by bone loss, further testing all small molecule agents described in TRANCE/RANK inhibition assays and in osteoclastogenesis inhibition assays and/or osteoclast function assays). Genetech, 108 F.3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Accordingly the claims are evaluated as being drawn to a method of treating patients who have diseases characterized by bone loss comprising administering an amount of TRANCE/RANK inhibitors effective to inhibit osteoclastogenesis and/or osteoclast function, wherein the TRANCE/RANK inhibitor is the peptidomimetic WP9QY, OPG polypeptide(s), and/or the anti-sense agents described by Baker et al.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Boyle et al. (EP0784093).

Boyle et al. teaches a secreted polypeptide (termed osteoprotegerin-OPG), which is a member of the TNF superfamily, involved in the regulation of bone metabolism (see abstract). On page 3, Boyle et al. describe that methods of treating bone diseases such as osteoporosis, hypercalcemia, Paget's disease of bone, and bone loss due to rheumatoid arthritis or osteomyelitis are possible by administration of the polypeptides and/or via anti-sense or gene therapy. On page 6, Boyle et al. teach that OPG appears to regulate a receptor-ligand interaction in the osteolytic pathway and the regulation appears to result in a reduction in the number of osteoclasts.

Pharmaceutical compositions comprising OPG nucleic acids and polypeptides are also encompassed anticipating "A method of treating patients who have diseases characterized by bone loss comprising the step of administering to said patient an amount of TRANCE/RANK inhibitors effective to inhibit osteoclastogenesis and/or osteoclast function" of claim 1.

The examiner respectfully points out the following from MPEP § 2112.01: "[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." Atlas Powder Co. v. Ireco Inc., 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. In re Best, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977).

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leonard M. Williams whose telephone number is 571-272-0685. The examiner can normally be reached on MF 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LMW

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER